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Review

Cardiovascular screening in Williams syndrome

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ABSTRACT

William's syndrome is a genetic disorder that is associated with a spectrum of cardiovascular disease: congenital heart disease, vascular disease, coronary artery disease, hypertension and arrhythmias. Patients may be at risk of significant morbidity and mortality over their lifetime including a risk of sudden cardiac arrest. Williams syndrome patients may develop progressive multi-site arterial stenosis, systemic hypertension, valve dysplasia, and arrhythmias with advancing age. They should always be considered at risk of having underlying coronary disease prior to anesthesia. Standard screening includes a comprehensive physical exam, electrocardiogram, and echocardiogram; however advanced cardiac imaging with computed tomography and/or magnetic resonance angiography may be beneficial to fully assess the vascular tree. We will review a systematic approach for clinicians caring for Williams syndrome patients to use for the detection of overt and subclinical forms of cardiovascular disease, especially prior to procedures requiring general anesthesia.

1. Introduction

Williams syndrome is associated with a 25–100 times greater risk of mortality compared to the general public [1–3]. Cardiovascular disease is present in > 90% of infants with Williams syndrome and is the leading cause of morbidity and mortality [4]. Williams syndrome patients are at high risk for sudden cardiac arrest (1/1000 patient-years) during procedures that require sedation or general anesthesia usually secondary to coronary ischemia or arrhythmias [3]. All clinicians (primary care, emergency medicine, cardiologists, anesthesiologists, nephrologists, gastroenterologists, ophthalmologists, neurologists, pulmonologists, endocrinologists, otolaryngologists, audiologists, radiologists, surgeons, and other sub-specialists) that provide medical care for Williams syndrome patients need to be familiar with the various forms of associated cardiovascular disease; and how to minimize cardiovascular morbidity and mortality.

Williams syndrome is caused by a microdeletion syndrome that results from the loss of approximately 26–28 genes in chromosome 7 (7q11.23) [4]. This genetic disorder affects the entire body and is typically associated with mild to moderate developmental delay, characteristic facial and eye features, hearing loss, behavioral issues including anxiety and attention deficit disorder, endocrinopathies including hypercalcemia, renal, musculoskeletal and gastrointestinal issues [5]. From a cardiovascular perspective, the gene deletion most frequently implicated in Williams syndrome is the elastin gene (ELN), which is located within the most commonly deleted region on chromosome 7. ELN encodes the precursors for a mature protein called elastin [6]. Elastin is the major component of elastic fibers within the extracellular matrix of a cell and provides the ability for distensibility and recoil in a wide range of tissues throughout the body [6]. The cardiovascular system is almost universally affected in Williams syndrome because elastin is a critical protein for the development of the heart valves and vascular system. Elastin comprises approximately 50% of the dry weight of the aorta and is found throughout the arterial system [4]. Reduction in the quantity or quality of elastin leads to arterial stenoses as well as increased stiffness of the vascular walls and heart valves [4,6]. The most common cardiovascular abnormality in Williams syndrome is supravalvar aortic stenosis [4]. Jiao et al. have studied supravalvar aortic stenosis in animal models and discovered that elastin deficiency predisposes to loss of circumferential growth in the aorta due to decreased elastic fibers, medial fibrosis, increased collagen deposition and smooth muscle cell hyperplasia [7]. This process may lead to arterial stenoses throughout the vascular tree, including the coronary arteries.

Cardiovascular disease exists within the continuum of life and is present from the womb to adulthood. Maturational changes occur

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Table 1
Five segment cardiovascular assessment of Williams syndrome.

Segment	Abnormalities commonly found in Williams syndrome	Ancillary testing to consider
Intracardiac anatomy screening	Congenital Heart Disease -Atrial septal defect -Ventricular septal defect -Other Valve dysplasia (please note these may progress with age) -Tricuspid dysplasia -Pulmonary valve dysplasia -Mitral valve prolapse -Mitral valve: prolapse, stenosis or regurgitation -Aortic valve dysplasia: stenosis or regurgitation Ventricular assessment -Left ventricular hypertrophy -Regional wall motion abnormality. -Systolic function: normal or abnormal	Transthoracic echocardiogram
Systemic arteriopathy screening	Pulmonary arteriopathy -Supravalvar pulmonary stenosis -Peripheral pulmonary stenosis: right and/or left Systemic arteriopathy -Supravalvar aortic stenosis -Transverse arch hypoplasia -Carotid artery stenosis -Coarctation of the aorta -Middle aortic syndrome -Mesenteric/cerebral stenosis -Renal artery stenosis -Femoral/iliac stenosis -Other	Consider computed tomography or magnetic resonance angiography
Coronary arteriopathy screening	Clinical symptoms: -Infant: diaphoresis or dyspnea with feeds, failure to thrive -Child/adult: chest pain, diaphoresis, syncope or dyspnea with exertion Abnormal Electrocardiogram -Ischemic changes: Q-waves, ST segments, T-waves Abnormal Echocardiogram -Decreased systolic function -Regional wall motion abnormalities -Hypoplasia of the right or left coronary artery -Unable to fully visualize color flow in the right or left coronary artery -Supravalvar aortic stenosis	Consider computed tomography angiography of the coronary arteries
Hypertension screening	Three limb blood pressure (both arms/leg) in all patients to exclude coarctation or middle aortic syndrome Blood pressure > 90th percentile for age and height Left ventricular hypertrophy seen on echocardiogram without evidence of left ventricular outflow tract obstruction	-Schedule cardiology and nephrology consultation -Basic metabolic panel and urinalysis -Renal ultrasound with Doppler -Consider 24-hour ambulatory blood monitor -Consider magnetic resonance angiography or computed tomography angiography of the abdomen to exclude renal artery stenosis.
Electrical conduction System screening	QTc interval prolongation with age Premature ventricular contractions Paroxysmal ventricular tachycardia	Electrocardiogram Holter monitor

within the cardiovascular system due to the deficiency of elastin and premature loss of elastin with advancing age [8]. These changes lead to increased stiffness in the vessel walls (hypertension) and stiffness of the heart valves (stenosis or regurgitation). All patients with Williams syndrome require a thorough cardiovascular assessment in order to detect clinically active or subclinical cardiovascular disease at all ages. The American Academy of Pediatrics has recommended that patients have three limb blood pressures (both arms and one leg), a complete physical exam, an electrocardiogram, and an echocardiogram with Doppler flow studies during the initial visit [9]. Infants should be followed every 3 months during the first year of life and annual visits are recommended through middle childhood [9]. If clinicians detect decreased peripheral pulses, carotid or abdominal bruits or echocardiograms reveal diffuse thoracic aortic stenosis then patients should undergo advanced cardiac imaging [9]. This may require a computed tomography, magnetic resonance angiography or cardiac

Table 2
Frequency of congenital heart disease in Williams syndrome.

Structural abnormality	Frequency
Supravalvar aortic stenosis	35–65%
Peripheral pulmonary stenosis	37–61%
Ventricular septal defects	8–21%
Mitral valve dysplasia (prolapse/regurgitation)	20%
Coronary artery abnormalities (ostial stenosis/dilations)	11–27%
Aortic valve dysplasia (bicuspid aortic valve, stenosis or regurgitation)	18%
Supravalvar pulmonary stenosis	12%
Atrial septal defects	3–6%
Ebstein's anomaly of the tricuspid valve, tetralogy of Fallot, total anomalous pulmonary venous return, complete atrioventricular canal, aorto-pulmonary window, interrupted aortic arch, pulmonary artery sling.	Rare

Adopted from Collins RT. Cardiovascular Disease in Williams Syndrome. Current Opinion-Pediatrics. 2018.

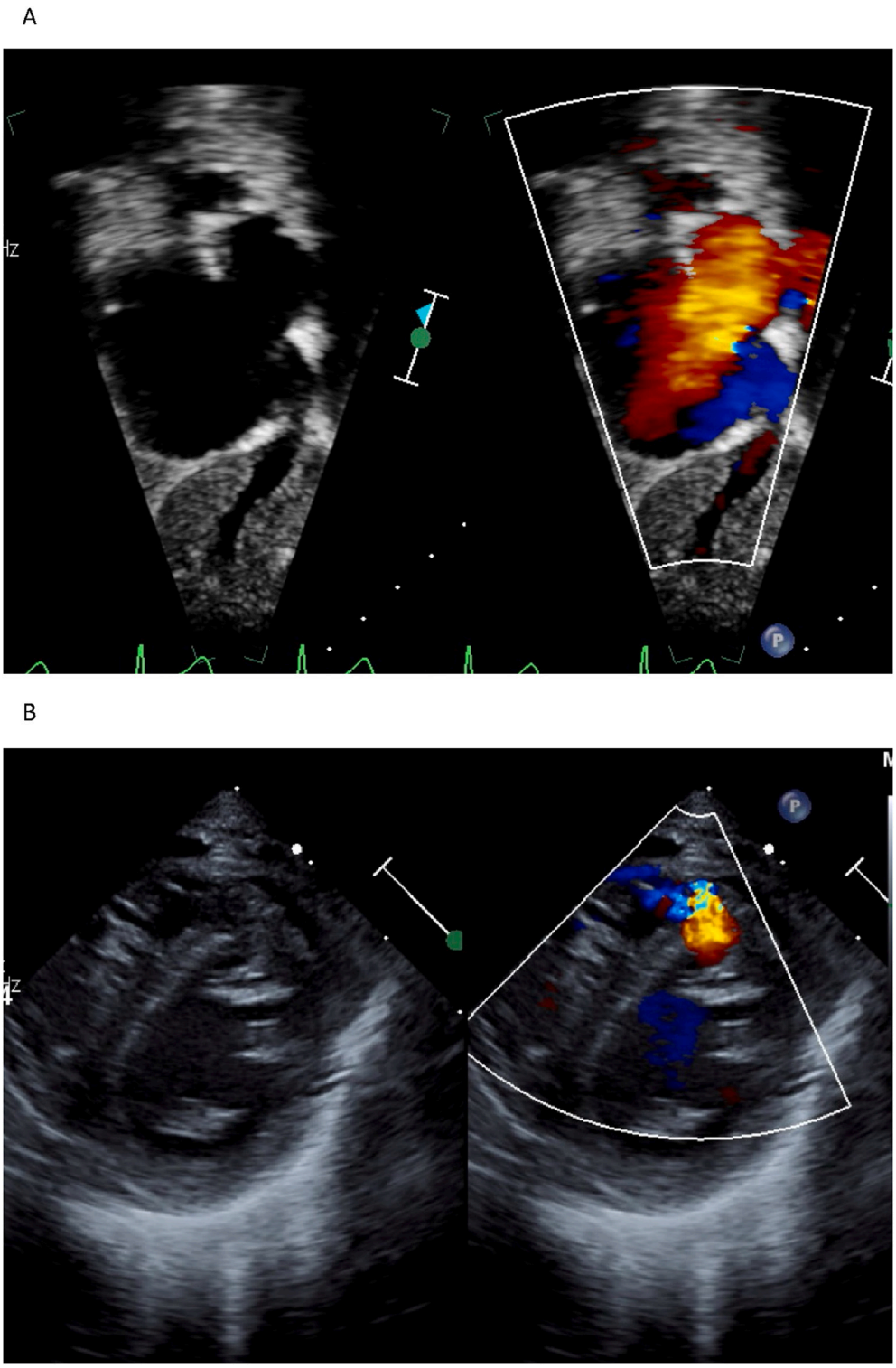


Fig. 1. A. Transthoracic echocardiogram in a subcostal bicaval view with a large secundum atrial septal defect.
B. Transthoracic parasternal short axis view with a small mid-muscular ventricular septal defect.

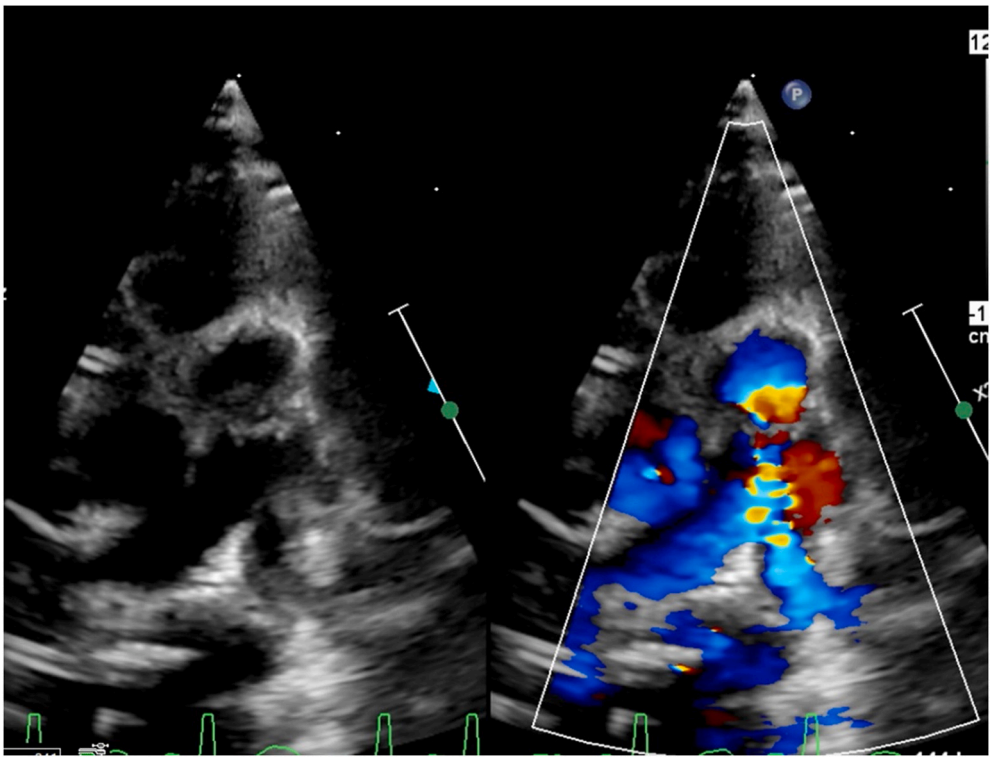


Fig. 2. Transthoracic parasternal short axis view demonstrating a dysplastic pulmonary valve with thickened leaflets that dome, severe stenosis and associated left pulmonary artery stenosis.

catheterization. These recommendations do not specifically address the need for an assessment for occult coronary artery abnormalities (ostial stenosis, diffuse coronary hypoplasia or stenosis, or coronary dilations), assessment for arrhythmias that may predispose to sudden cardiac arrest or need for longitudinal cardiovascular follow-up in adolescents and adults with Williams syndrome.

Below we will present our single center approach for cardiovascular screening in Williams syndrome. Nemours Children's Hospital in Orlando, Florida is a free-standing children's hospital and serves as a regional tertiary referral center. The hospital is part of a larger national enterprise that includes our sister hospital AI Dupont Hospital for Children in Wilmington, Delaware and Nemours Specialty Care Clinics in Pensacola, Florida. We have hosted a biannual regional multispecialty Williams syndrome clinic since 2016 for the southeast United States and are one of only 11 dedicated clinics in the United States as listed on the Williams syndrome website - https://williams-syndrome.org/parent/williams-syndrome-clinics. Our center offers a multi-disciplinary team approach that includes genetics, cardiology, cardiac anesthesia, radiology, nephrology, urology, endocrinology, gastroenterology, nutrition, ophthalmology, otolaryngology, audiology, pulmonology, neurology, orthopedic surgery, neurosurgery, and general surgery with additional subspecialists available upon request. We follow over 70 patients with Williams syndrome and utilize a Ronald McDonald House for families traveling any extended distances. All procedures requiring sedation or anesthesia are performed with dedicated cardiac anesthesiologists. This review will provide caregivers a structured approach to cardiovascular screening as well as discuss the role of echocardiography and advanced cardiac imaging (computed tomography and magnetic resonance angiography) during the initial screen and long-term follow up of patients with Williams syndrome.

Our approach to comprehensive cardiovascular screening in Williams syndrome involves four primary premises:

1. The arteriopathy in Williams syndrome may affect more than one site
2. All Williams syndrome patients are considered at risk for occult coronary artery disease with an inherent risk of sudden cardiac arrest, especially during anesthesia
3. Williams syndrome patients are at risk of developing hypertension with advancing age
4. Longitudinal follow-up is required in Williams syndrome patients due to the risk of maturational cardiovascular disease (hypertension, valve dysplasia, and arrhythmias)

Our typical visit includes a detailed personal history and review of systems for active cardiovascular symptoms, as well as a thorough past medical history, past surgical history, family history, and social history. During the exams and ancillary testing, many patients with Williams syndrome will have significant anxiety and may be uncooperative related to the developmental delays and anxiety. Use of child life, television, or portable electronics may be helpful distractors. The exam should include comprehensive vital signs including four limb blood pressures (utilizing manual blood pressures when needed), thorough cardiovascular physical exam with assessment of distal pulses in all four extremities, auscultation for bruits in the neck and abdomen, electrocardiogram and an echocardiogram with Doppler flow assessment.

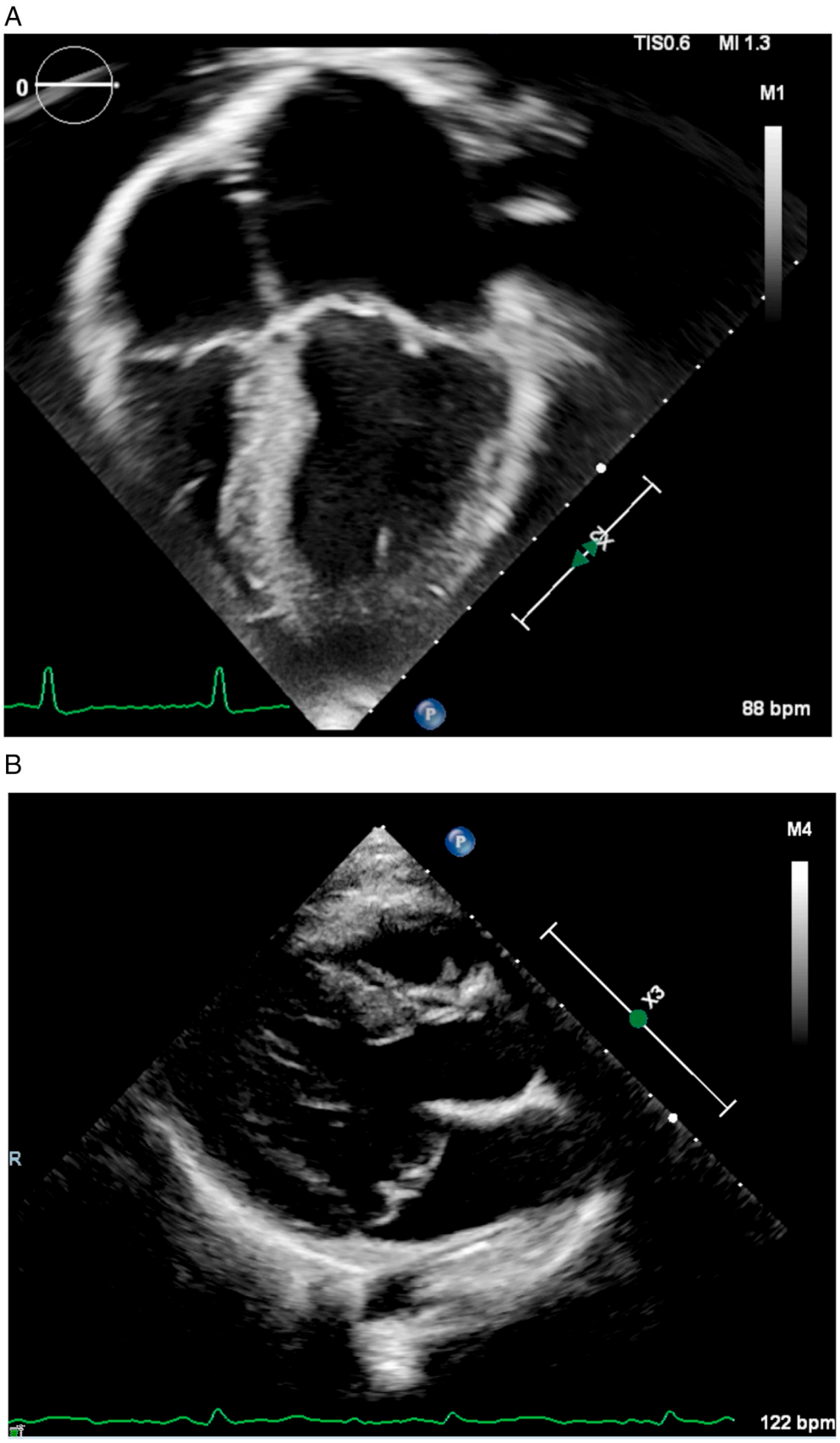
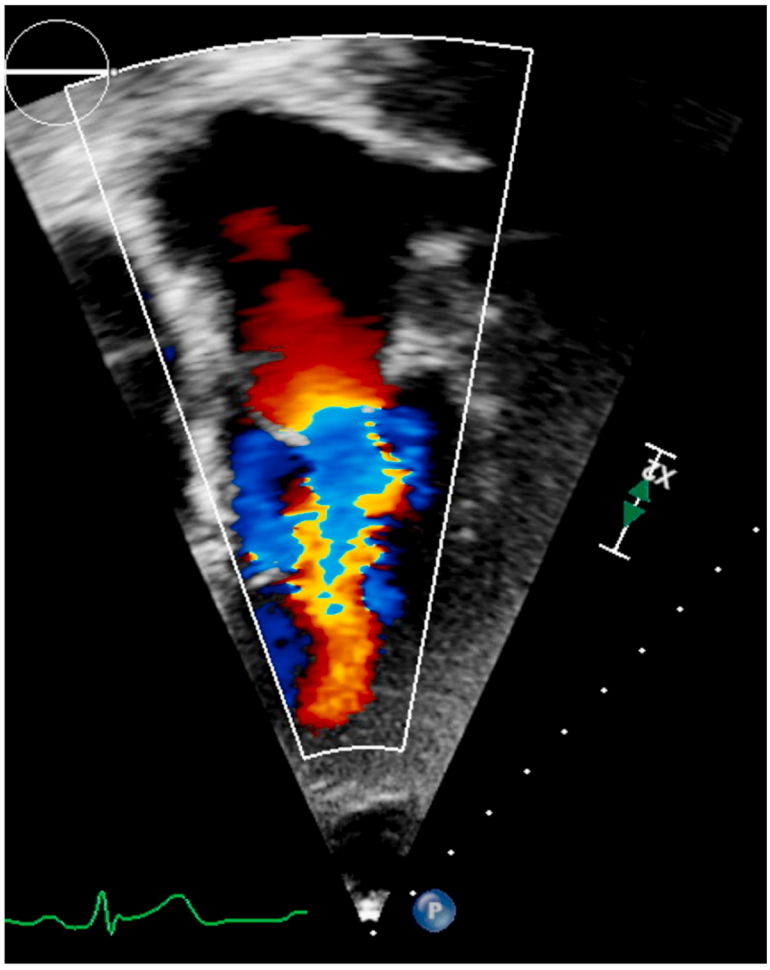


Fig. 3. A. Apical four chamber view showing prolapse of the anterior leaflet of the mitral valve.
B. Parasternal long axis view showing prolapse of the anterior leaflet of the mitral valve.
C. Apical four chamber view of a 25 year old patient with Williams syndrome and mitral valve stenosis.
D. Doppler assessment of the mitral valve demonstrates a peak gradient of 18 mmHg and mean gradient 11 mmHg.

C



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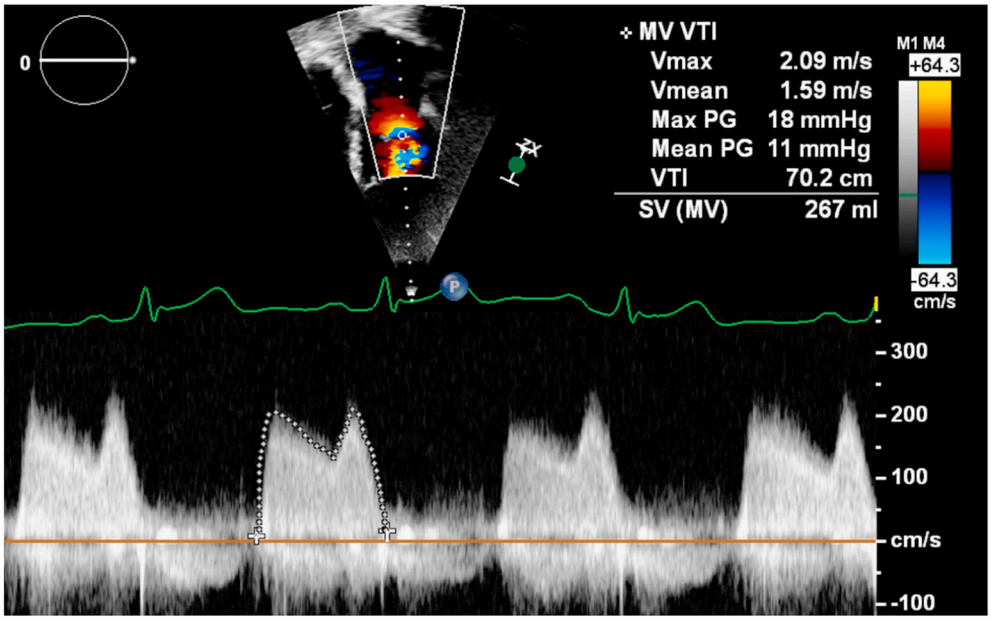

Fig. 3. (*continued*)

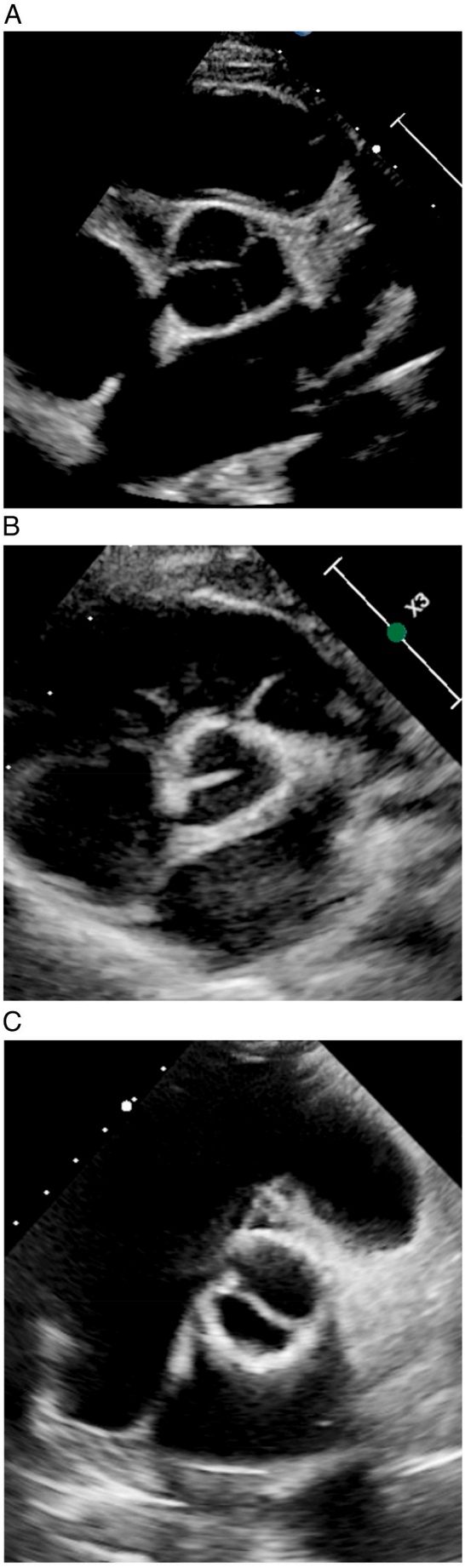

Fig. 4. Parasternal short axis imaging of the aortic valve (A) normal trileaflet aortic valve, (B) aortic valve dysplasia with partial fusion of the right and non-coronary cusps and (C) a bicuspid aortic valve.

Advanced cardiac imaging with computed tomography or magnetic resonance angiography is added for a clinical suspicion of systemic arteriopathy, coronary arteriopathy, or if hypertension is noted. The decision as to which study is best depends on the clinical context. Computed tomography provides higher resolution images of the coronary anatomy and vascular tree at the expense of exposure to ionizing radiation. Cardiac magnetic resonance imaging can provide great visualization of the vascular tree, assess flow properties, and provide functional information. Imaging of the coronaries by cardiac magnetic resonance imaging is inferior to computed tomography but may be improved with optimal conditions. The need for longer imaging times, possible sedation and anxiety relative to the scanner often factors into the decision of one versus the other. As such, each patient is considered individually when considered advanced cross-sectional imaging for clinical guidance and management. Ambulatory 24-hour blood pressure monitors, Holter monitors, event monitors, and stress test are also utilized in age appropriate patients with clinical indications. All clinicians should segmentally assess the cardiovascular system in Williams syndrome. One helpful mechanism is to consider the cardiovascular system in the following five segments (Table 1):

- Intracardiac anatomy
- Systemic arteriopathy
- Coronary arteries
- Hypertension
- Electrical conduction system

2. Intracardiac anatomy assessment

The intracardiac anatomy is best assessed by a transthoracic echocardiogram. Our institutional protocol for pediatric echocardiograms is fully described by Madueme et al. “Segmental Approach Segmental Approach to Performing a Standard Pediatric Echocardiogram” [10]. In Williams syndrome, the intracardiac assessment of the heart can be separated into three components: assessment for congenital heart disease, valvular dysplasia, and ventricular function. The frequency of congenital heart disease in Williams syndrome is listed in Table 2 [4]. Septal defects are frequently seen in Williams syndrome, Fig. 1A demonstrates a secundum atrial septal defect; and Fig. 1B ventricular septal defect. Other forms of more complex congenital heart disease may occur less frequently and are listed in Table 2 [4]. The assessment of the heart valves is a critical component of any echocardiogram performed in a Williams syndrome patient. The tricuspid valve is usually normal; however, tricuspid valve dysplasia with tricuspid regurgitation at varying degrees can be seen including the most severe form, Ebstein's anomaly of the tricuspid valve. The pulmonary valve frequently has stenosis or regurgitation (Fig. 2). The mitral valve in infants is typically normal, but with advancing age patients may demonstrate mitral valve prolapse and/or regurgitation. Some patients with Williams syndrome may also develop mitral valve stenosis as they age into adulthood. Fig. 3A, B, C, and D demonstrate common forms of mitral valve pathology in Williams syndrome. The normal aortic valve usually has three leaflets, but some individuals may have a bicuspid valve (two leaflets) or have dysplasia (fusion of the leaflets or thickening of the leaflets) that leads to progressive aortic valve regurgitation or stenosis overtime. Fig. 4A, B, C demonstrate these forms of aortic valve pathology. A transthoracic echocardiogram is also important for the assessment of the left ventricle. The presents of left ventricular hypertrophy typically suggest long standing systolic hypertension and/or various forms of left ventricular outflow tract obstruction. Functional assessment of the left ventricle is fully described by Tsuda et al.

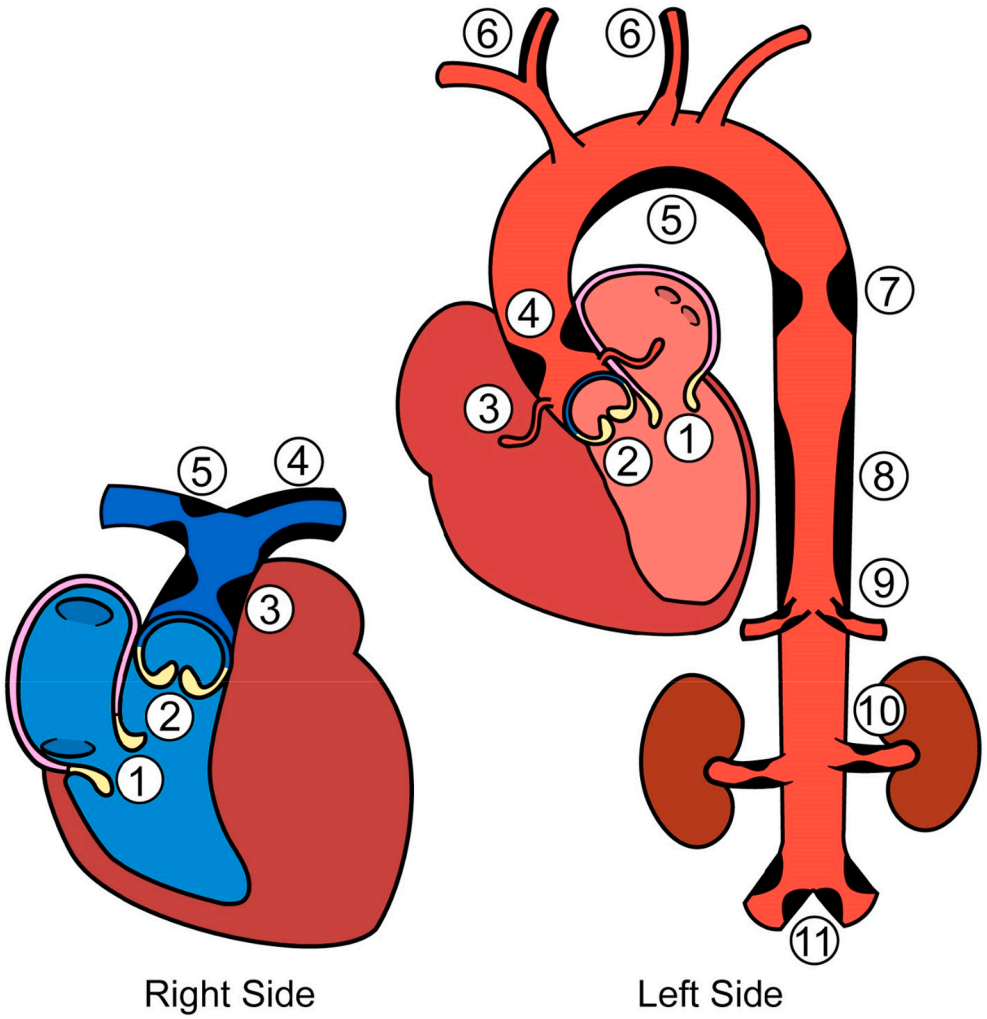

Fig. 5. The elastin deficiency in Williams syndrome may lead to progressive valve dysplasia and a systemic arteriopathy that may affect both the right and left sides of the heart. Right side heart structures include (1) tricuspid valve, (2) pulmonary valve, (3) supravalvar pulmonary stenosis, and (4) diffuse peripheral pulmonary artery hypoplasia (5) focal peripheral pulmonary stenosis. Left sided heart structures include: (1) mitral valve, (2) aortic valve, (3) coronary artery stenosis, hypoplasia or dilations, (4) supravalvar aortic stenosis, (5) transverse aortic arch hypoplasia, (6) carotid artery stenosis, (7) coarctation of the aorta, (8) middle aortic syndrome, (9) mesenteric or celiac artery stenosis, (10) renal artery stenosis, (11) iliac or femoral artery stenosis.

"Functional assessment of the left ventricle" [11]. If a Williams syndrome patient is found to have new onset systolic dysfunction (decrease in ejection fraction/shortening fraction) or regional wall motion abnormalities, a clinician should be highly suspicious of underlying coronary artery disease.

3. Systemic arteriopathy assessment

After complete assessment of the intracardiac anatomy, a clinician should turn their attention to surveillance for systemic arteriopathy. Fig. 5 - reviews the most common locations for vascular stenoses within the cardiovascular system in Williams syndrome. The clinician should ensure that the right and left ventricular outflow tracts are fully evaluated. The most common arterial stenoses in the right ventricular outflow tract are supravalvar pulmonary stenosis and peripheral pulmonary stenosis. Fig. 6A, B, and C demonstrates supravalvar pulmonary stenosis and peripheral pulmonary stenosis. An advanced imaging study (magnetic resonance angiogram or computed tomography angiogram) will be needed to completely assess the distal pulmonary vascular bed. Cha SG, et al. looked at the long-term cardiovascular outcomes of Williams syndrome and determined that most branched peripheral pulmonary stenosis, including severe forms, improve with age and may not need intervention [12]. Of those that require intervention for severe peripheral pulmonary stenosis, balloon angioplasty in the cardiac catheterization lab has a 75% recurrence rate at 5 years and stent implantation may develop neo-intimal hyperplasia [4]. Therefore, multilevel surgical pulmonary artery reconstruction has been recommended as first line management at some institutions [4].

In contrast to the right side of the heart, arterial stenoses on the left side of the heart can progress with age [12,13]. Reduced elastin formation may result in wide-spread arteriopathy on the left side of the heart [14]. The most common site for arterial stenosis is supravalvar aortic stenosis and occurs in up to 65% of patients with Williams syndrome [4]. Mild to moderate degrees of supravalvar aortic stenosis (peak gradient < 50 mmHg) may remain stable or even regress with time, and not require surgical intervention [13]. However, moderate to severe degrees of supravalvar stenosis usually progress and will often require surgical repair at a median age 5.8 years but have a low risk of needing re-intervention [12]. Fig. 7A, B and C demonstrate supravalvar aortic stenosis with the typical "hourglass" configuration by

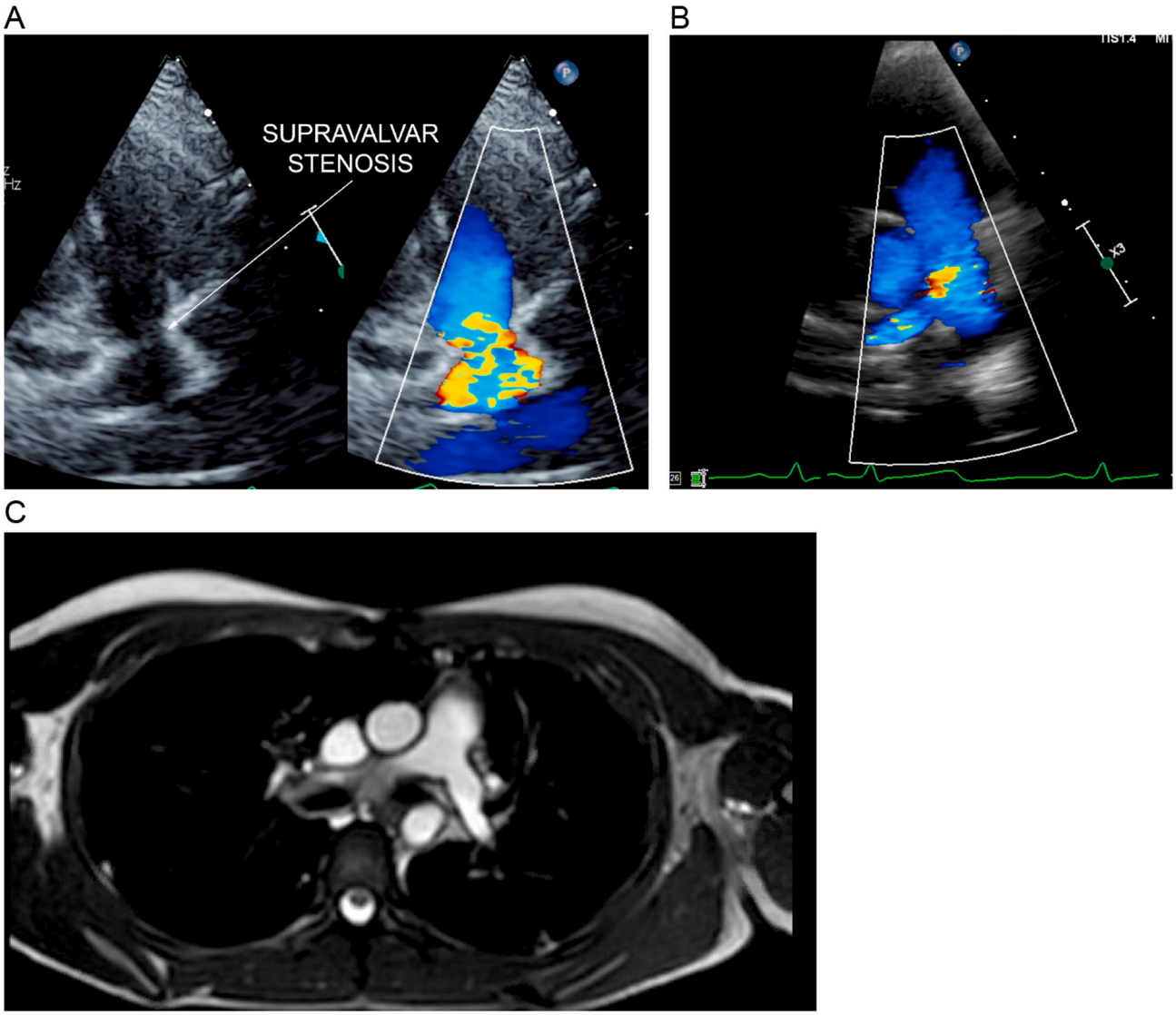

Fig. 6. A. Parasternal short axis view of supravalvar pulmonary stenosis in two dimensional imaging and with color Doppler assessment.
B. Williams syndrome patient with right pulmonary artery hypoplasia in a parasternal short axis plane.
C. Magnetic resonance imaging of the left pulmonary artery demonstrating distal peripheral pulmonary artery stenosis.

echocardiography and magnetic resonance imaging. Transthoracic echocardiography is usually excellent at imaging the ascending and descending thoracic aorta but limited assessment of the distal aortic vasculature due to poor acoustic windows, lung artifact, or inability of the patient to cooperate. Full assessment of the vascular system is best achieved with an advanced imaging study (magnetic resonance angiogram or computed tomography angiogram). Indications include: need for further anatomical delineation after an echocardiogram; transthoracic echocardiography detects any significant stenoses on the left side especially diffuse hypoplasia of the thoracic aorta and the clinician wants to perform surveillance for more distal stenosis; or new clinical symptoms develop (arm to leg blood pressure differentials, hypertension, bruits or diminished pulses in an extremity) that are not explained by echocardiography. Hills et al. determined that approximately 85% of advanced imaging studies in Williams syndrome will detect an abnormality [1]. All aspects of the vascular tree can be affected in Williams syndrome (Fig. 5) and may include: transverse arch hypoplasia, carotid artery stenosis, coarctation of the aorta (Fig. 8A and B), mesenteric/celiac artery stenosis (Fig. 9A and B), middle aortic syndrome (diffuse narrowing of the thoracic and abdominal aorta) and renal artery stenosis (Fig. 10) as well as iliac or femoral artery stenosis. Magnetic resonance imaging may also discover systemic venous abnormalities - Fig. 11 demonstrated a case of diffuse venous ectasia in a Williams syndrome patient [15].

4. Coronary artery assessment

Even though systemic arterial stenosis is more prevalent, discrete

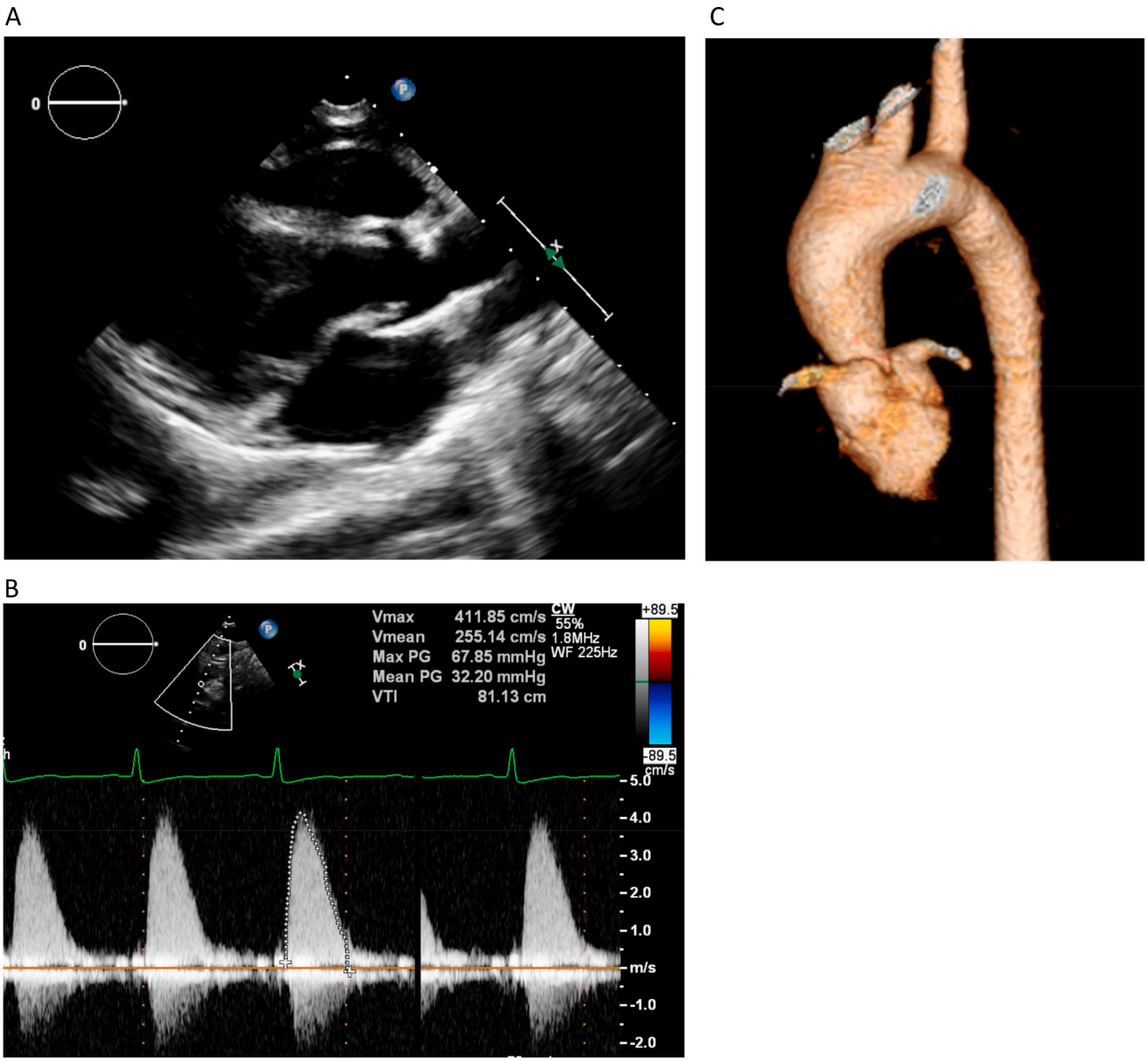

Fig. 7. A. Parasternal long axis with supravalvar aortic stenosis in the typical "hour glass" configuration.
B. Suprasternal pulse Doppler pattern in ascending aorta in a patient with supravalvar aortic stenosis demonstrating a peak gradient 67 mmHg and mean gradient 32 mmHg.
C. Magnetic resonance imaging demonstrating discrete supravalvar aortic stenosis in a patient with Williams syndrome. Please note that the coronary arteries originate at the level of the stenosis.

coronary artery abnormalities may have more devastating complications. Coronary osteal stenosis, abnormal coronary orifices (slit like opening), diffuse hypoplasia of a coronary artery or coronary dilations are the most common abnormalities found and the major etiology of intra-operative morbidity and mortality [16]. Coronary abnormalities can occur independently or with the presence of supravalvar aortic stenosis. It is estimated that 11–27% of Williams patients will have a coronary abnormality, but this is likely an underestimate as occult coronary disease may go undetected in this population [4]. In the presence of supravalvar aortic stenosis, coronary artery abnormalities have been noted in up to 60% of Williams syndrome patients including diffuse tortuosity, medial hypertrophy, and fusion of the left aortic sinus leading to obstruction of the left coronary artery [17]. Williams syndrome patients should be assessed for coronary artery disease, especially before undergoing procedures that require anesthesia. The benefits of the procedure should out-weight the potential risk of sudden cardiac arrest. Clinicians should especially remember this before scheduling testing or minor procedures that require anesthesia (audiology exams, ophthalmologic exams, dental exams, endoscopy, colonoscopy, tympanostomy tubes, hernia surgeries, or orthopedic procedures). Induction of general anesthesia may decrease systemic blood pressure which can cause decreased coronary perfusion and myocardial ischemia

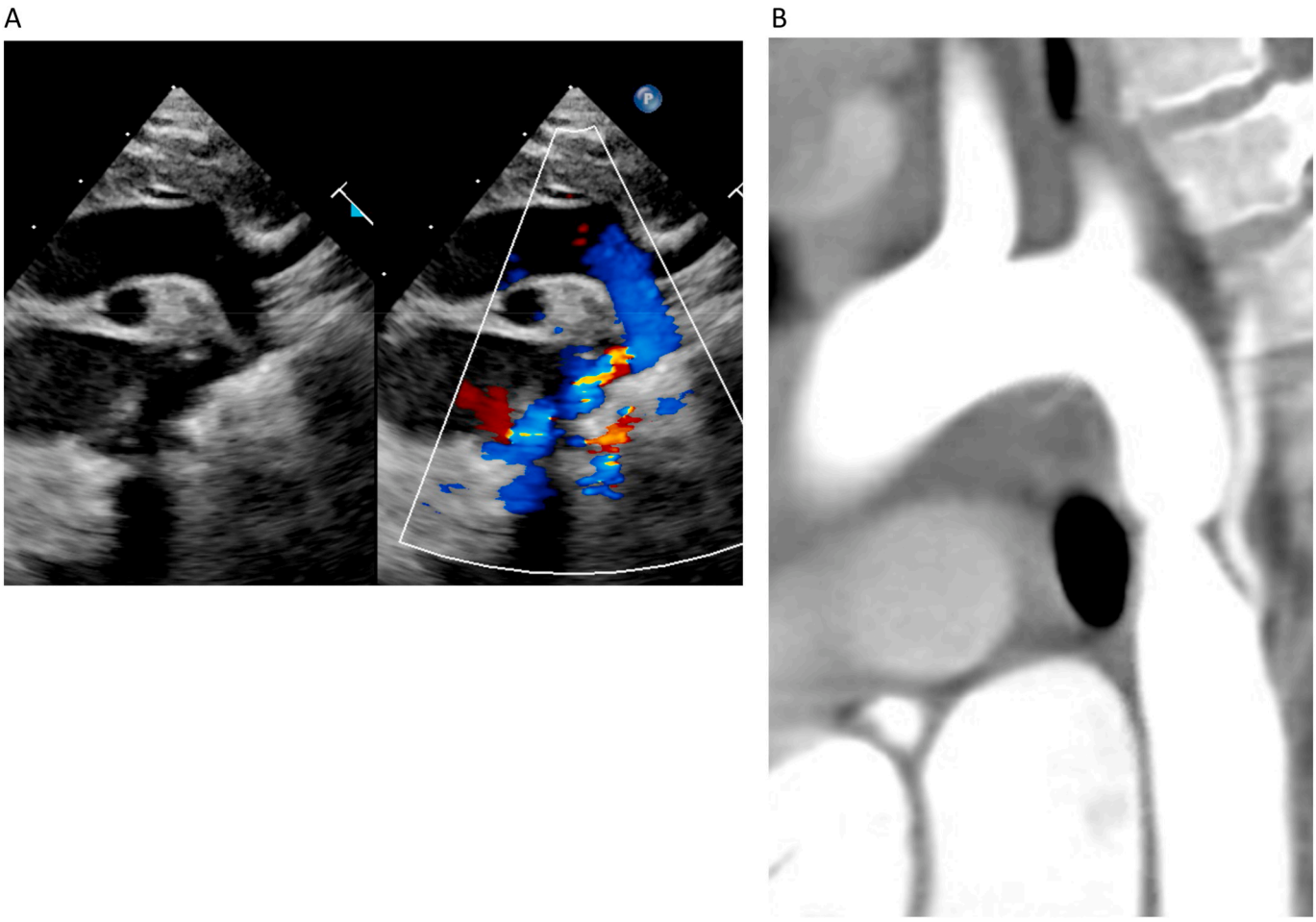

Fig. 8. A. Echocardiogram with suprasternal notch imaging showing discrete coarctation of the aorta in the juxtaductal region by two dimension and color Doppler assessment.
B. Magnetic resonance imaging demonstrating a discrete coarctation in the aorta.

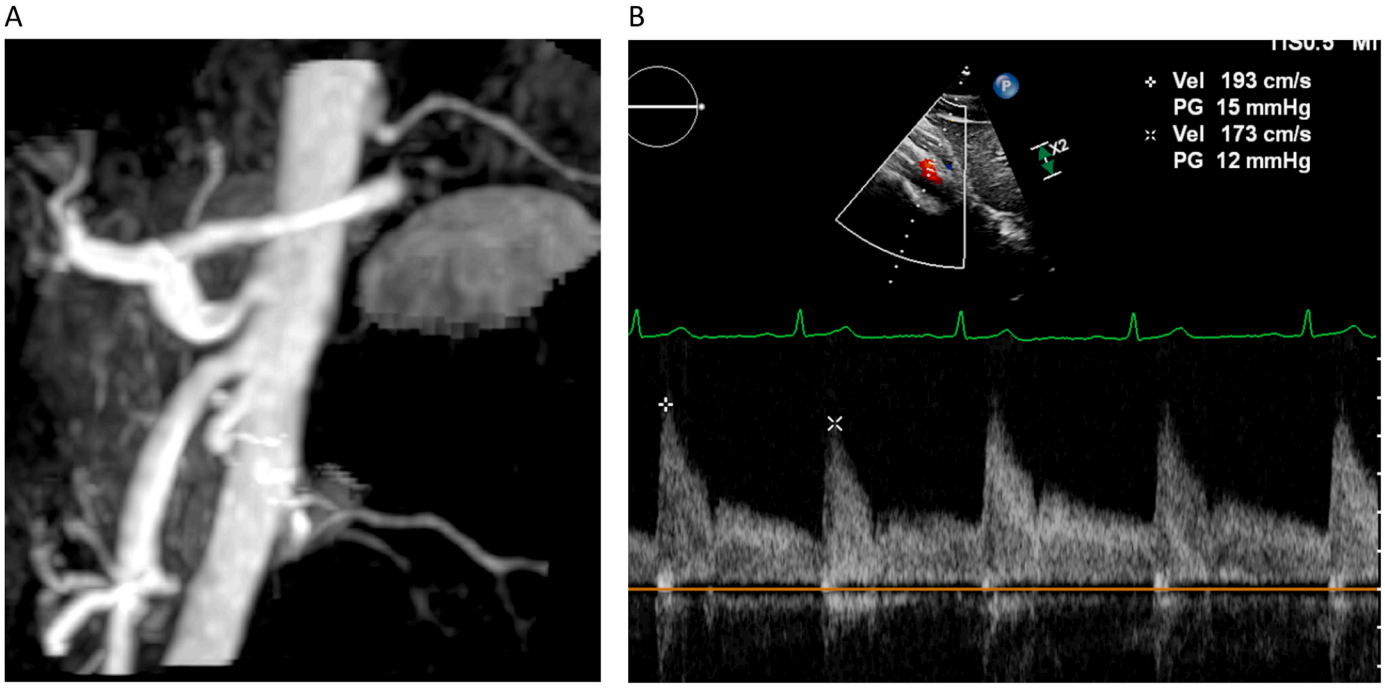

Fig. 9. A. Computed tomography angiography demonstrating celiac artery stenosis.
B. Ultrasound with pulse Doppler of the celiac artery.

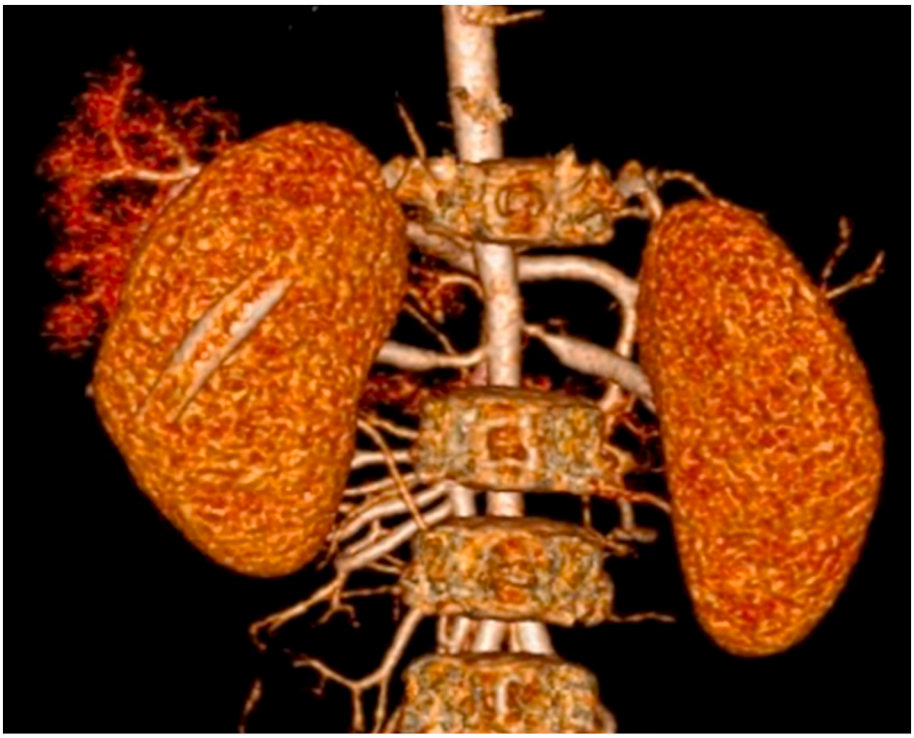

Fig. 10. A three year old child with Williams syndrome who presented with new onset hypertension. Computed tomography angiography demonstrates middle aortic syndrome with hypoplasia of the abdominal aorta and bilateral renal artery stenosis.

if underlying coronary abnormalities are present. Pre-operatively all patients should be screened with a transthoracic echocardiogram, which should fully assess the coronary bed including the origin of the right and left coronary artery, size of the coronary arteries with z-scores, and color Doppler of the flow within the coronary arteries. Size discrepancies between the proximal right and left coronary artery should always alert clinicians to the possibility of a coronary stenosis. Anesthesia risk stratification has been suggested by Collins RT 2018 and high-risk candidates include those with [4]:

1. Age < 3 years old
2. History of prior adverse cardiovascular events
3. Preprocedural arrhythmias
4. Moderate to severe bilateral outflow tract obstruction
5. Supravalvar aortic stenosis gradient > 40 mmHg
6. Known coronary artery involvement
7. Diffuse stenosis of the thoracic aorta
8. Right ventricular pressure > 75% systemic pressure
9. Moderate to severe right or left ventricular hypertrophy
10. Electrocardiogram with evidence of ischemia or QTc prolongation > 500 milliseconds

Every patient with Williams syndrome should be considered at high risk for coronary ischemia with anesthesia and/or sedation, even those with normal pre-operative coronary studies since death has occurred even in the absence of structural abnormalities [18]. Anesthesia should be performed within a hospital with an intensive care unit and extracorporeal membrane oxygenation (ECMO) as resources due to these risks. Anesthesia protocols with pre-operative testing, intravenous fluid hydration, medication choices for induction of anesthesia and post-operative monitoring have been utilized in this high risk cohort. At our institution, we require an electrocardiogram and echocardiogram within 6 months of a diagnostic or therapeutic procedure requiring anesthesia with further testing (CT angiography) if abnormalities of the coronary arteries are noted by echocardiography. Computed tomographic angiography is the non-invasive gold standard for complete assessment of the coronary arteries. It is able to three-dimensionally assess the coronary orifices to exclude osteal stenosis and evaluate the entire length of the coronary arteries for stenosis. A computed tomography angiogram should be considered in the presence of supravalvar aortic stenosis, diffuse hypoplasia of the thoracic aorta, inability to fully delineate the anatomy of the coronary arteries, a size discrepancy of the proximal coronary arteries is present on echocardiography, abnormal ventricular function is noted on a transthoracic echocardiogram (decreased ejection fraction, shortening fraction or regional wall motion abnormalities), history of paroxysmal ventricular tachycardia, or evidence of ischemia on either electrocardiography or a stress test (T-wave inversions, ST elevations/depressions or pathological Q-waves). Fig. 7C demonstrates the close proximity of the coronary artery origins to the supravalvar aortic stenosis. If coronary abnormalities are noted on imaging studies, a cardiac catheterization with coronary angiography may be indicated. Case reports of coronary revascularization in the cardiac catheterization lab or surgical revascularization in the operating room have been documented [17,19].

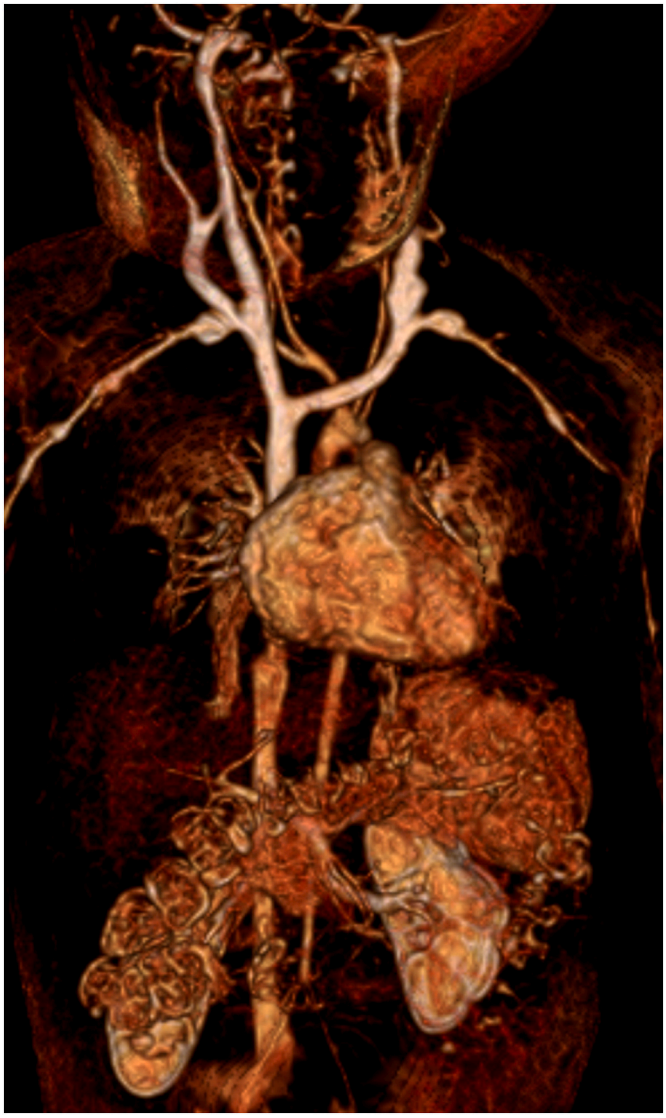

Fig. 11. Magnetic resonance imaging in a child with Williams syndrome and supravalvar aortic stenosis demonstrated occult venous ectasia of the large veins in the upper extremities and neck.

5. Assessment for hypertension

Hypertension is the most frequent cardiovascular problem encountered in individuals with Williams syndrome as they age into adulthood. It is also most often detected in the ambulatory setting by primary care, subspecialists, or emergency medical physicians. The American Academy of Pediatrics estimates that hypertension is present in 50% of Williams syndrome patients and may occur at any age. In the general public, the American Heart Association 2020 Report on Heart Disease and Stroke Statistics estimates that 11% of children and 46% of adults in the United States have hypertension or borderline high blood pressure [20]. Aging causes degradation of elastic fibers within the arterial network, which promotes increased vascular stiffness as collagen replaces the elastic fibers [8,21]. These maturational changes lead to increased pulse pressure within the vascular system and micovasculature injury in the end organs (brain, eyes, heart, and kidney) [8,21]. Hypertension is a final common pathway of the increased arterial stiffness and progressive end-organ injury of the kidney. Elastin deficiency may produce structural defects in the kidney that affect the glomerular filtration barrier [4]. Blood pressure screening in children usually starts at age 3 years; except for high risk populations with conditions such as prematurity < 32 weeks, congenital heart disease, recurrent urinary tract infections, congenital renal or urological malformations, family history of congenital renal disease, solid organ transplant, malignancy or bone marrow transplant, medications that cause high blood pressure, systemic illnesses associated with hypertension or evidence of intracranial pressure. In these conditions, blood pressure screening should occur at every office visit after hospital discharge [22]. Williams syndrome is a systemic arteriopathy that is associated with hypertension, so blood pressure screening should start at the time of diagnosis and annually thereafter. Three limb blood pressures are recommended in both arms and one leg in order to exclude coarctation of the aorta, diffuse hypoplasia of the thoracic aorta and middle aortic syndrome in the initial visit by American Academy of Pediatrics guidelines [9], we, however, perform four extremity blood pressures at all visits and all ages because left heart disease may progress with age. Blood pressure acquisition in Williams syndrome patients can be challenging due to developmental delays, anxiety, and inability to cooperate. Many times, clinicians may want to perform or repeat blood pressures near the end of the visit with a manual cuff when patients have become more familiar with the clinic staff and environment [9]. This will avoid erroneously high blood pressure measurements that are taken when a patient may be anxious or upset. All patients with Williams syndrome need an abdominal ultrasound at the time of diagnosis to assess the kidneys and bladder. If hypertension is noted (blood pressure > 90th percentile for age and height) then cardiology and/or nephrology evaluation is indicated. Although hypertension in Williams syndrome may be secondary to the maturational changes described above, as many as 60% will have to renal artery stenosis as well [14]. Whenever hypertension is diagnosed, Williams syndrome patients should have a basic metabolic panel (electrolytes and BUN/creatinine), complete blood count, fasting blood glucose, urinalysis, urine culture, and renal ultrasound with Doppler. Renal ultrasounds in Williams syndrome may have false negative results. Hills et al. demonstrated that 11 patients with Williams syndrome who had renal ultrasounds with Doppler and were thought to be normal, however, advanced imaging showed that 45% (5/11) had true renal artery stenosis [1]. Clinicians should have a low threshold for advanced cardiac imaging (magnetic resonance or computed tomography angiography) to exclude renal artery stenosis [1]. Fig. 10 shows a computed tomography angiogram with bilateral renal artery stenosis. End-organ evaluation should also include an echocardiogram to assess for left ventricular hypertrophy and left ventricular outflow tract obstruction and an ophthalmological exam to assess the retinal vessels. Williams syndrome patients diagnosed with hypertension < 1 year of age are more likely to have diffuse hypoplasia of the aorta [1]. Therapy for hypertension should be directed by providers experienced in Williams syndrome as management with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers may lead to renal failure in the presence of bilateral renal artery stenosis. Ambulatory blood pressure monitors are helpful in determining the effectiveness of medical therapy but may be challenging in young patients due to the developmental delays and anxiety.

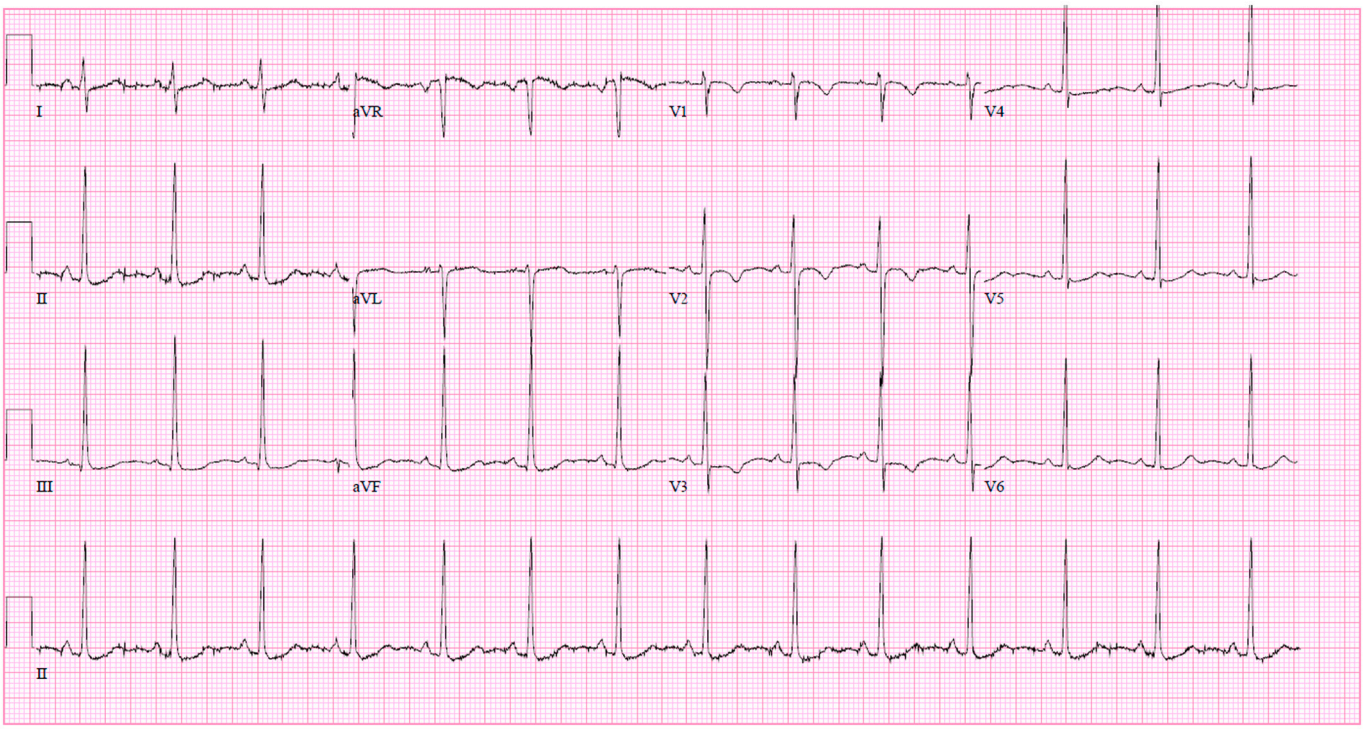

Fig. 12. Adult electrocardiogram performed in a patient with Williams syndrome demonstrating non-specific S-T changes and borderline QTc prolongation.

6. Assessment of the electrical conduction system

The elastin deficiency in Williams syndrome leads to anomalies in the macro-vasculature (medium and large arteries) and micro-vasculature (small arteries). Changes within the myocardial microvascular system, have been noted in other disease processes such as: hypertrophic cardiomyopathy, chronic hypertension, and ischemic heart disease [23]. These lead to microvascular dysfunction and decreased myocardial perfusion with progressive myocardial fibrosis, changes in ventricular repolarization on electrocardiogram and increased risk of ventricular ectopy/ventricular tachycardia [23]. QTc prolongation has been noted in 13% of Williams syndrome patients [23–25] In 2012 Collins et al., they reviewed longitudinal electrocardiograms from 26 patients at the Williams clinic at the Children's Hospital of Philadelphia [23]. They found that the QTc interval increased with age, increased with heart rate and severity of severe obstructive lesions [23]. Increased QTc intervals correlated with increasing ventricular ectopy [23]. Premature ventricular contractions were frequent in 81% of patients and 19% had non-sustained ventricular tachycardia [23]. Ventricular tachycardia was not associated with prior interventions of obstructive lesions and was non-torsade de pointes morphology in nature, suggesting this was not related to congenital prolongation of the QTc [23]. The median age of patients developing ventricular tachycardia was 21.9 years with a range of 8.1 to 39.7 years [23]. Clinicians must ensure the electrical conduction is routinely assessed in Williams syndrome patients as they age. Ambulatory electrocardiograms are performed at all visits and twenty-four hour Holter monitors are added if the QTc $>$ 450 milliseconds or annually when developmentally able to tolerate. During the pre-operative assessment of a Williams syndrome patient: a QTc $<$ 450 milliseconds is normal, QTc $>$ 450 but $<$ 500 milliseconds is moderate risk, and a QTc $>$ 500 milliseconds or with documented arrhythmias is considered high risk for an anesthesia related cardiac arrest [4]. Fig. 12 shows an electrocardiogram with non-specific S-T changes and borderline QTc prolongation, Fig. 13 Holter monitor with premature ventricular contractions and non-sustained ventricular tachycardia.

7. Conclusions

Williams syndrome is associated with an elastin deficiency that predisposes to widespread changes within the cardiovascular system. Life-long cardiovascular care is required. A five segment approach to the surveillance of the cardiovascular system (intracardiac anatomy, systemic arteriopathy, coronary arteries, hypertension, and electrical conduction system) is recommended to fully assess this patient population. The mainstay of routine surveillance is provided by a comprehensive physical exam, electrocardiogram and transthoracic echocardiogram, however, there is an ever increasing role for advanced cardiac imaging (magnetic resonance or computed tomography angiography) in Williams syndrome patients. Hopefully, the utilization of comprehensive screening to detect occult cardiovascular disease will reduce the morbidity and mortality for the Williams syndrome population in the future.

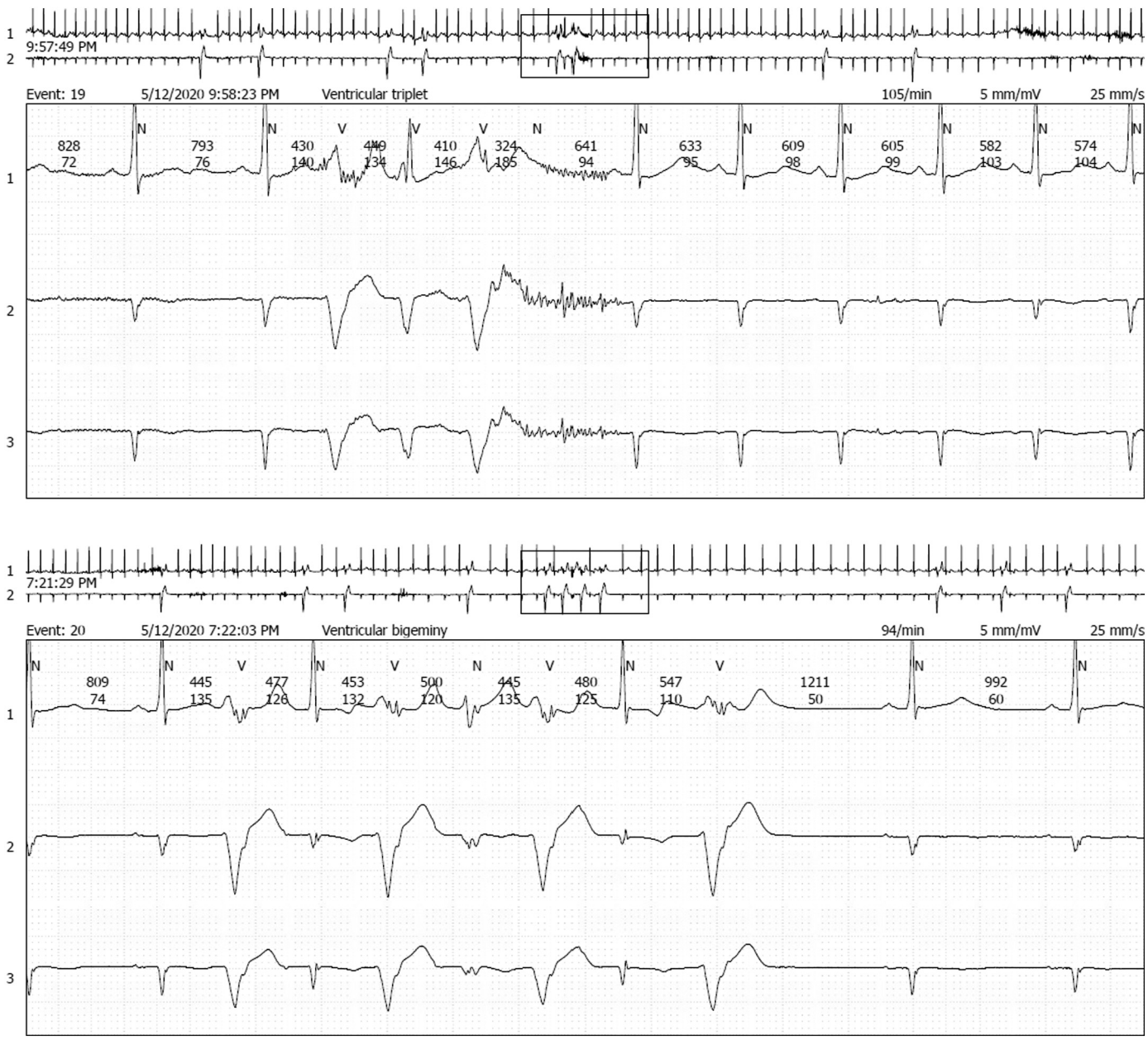

Fig. 13. Holter monitor demonstrating frequent premature ventricular contractions and non-sustained ventricular tachycardia.

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Declaration of competing interest

No conflicts of interest noted.

References

[1] Hills JA, Zarate YA, Danylchuk NR, Lepard T, Chi-Jen Chen J, Collins RT. Advanced cardiovascular imaging in Williams syndrome: Abnormalities, usefulness and strategy for use. Am J Med Genet A 2017 May;17395:1194–9. https://doi.org/10.1002/ajmg.a.3813828332295.

[2] Collins RT. Cardiovascular disease in Williams syndrome. Circulation 2013;127:2125–34.

[3] Wessel A, Gravehorst V, Buchhorn R, Gosch A, partsch CJ, Pankau R. Risk of sudden death in the Williams-Beuren syndrome. Am J Med Genet A 2004 Jun 15;127A(3):234–7. https://doi.org/10.1002/ajmg.a.30012. PMID15150772.

[4] Collins RT. Cardiovascular disease in Williams syndrome. Curr Opin Pediatr 2018 Oct;3(95):609–15. https://doi.org/10.1097/MOP.0000000000000064. PMID 30045083.

[5] Walton JR, Martens MA, Pober BR. The proceeding of the 15th professional conference on Williams syndrome. Am J Med Genet 2017;173A:1159–71. https://doi.org/10.1002/ajmg.a.3815628371210.

[6] Duquelasio ML, Kozel BA. Elastin-driven genetic disease. Matrix Biol 2018 Oct;71–72:144–60. https://doi.org/10.1016/j.matbio.2018.02.02129501665.

[7] Jiao Y, Li G, Korneva A, et al. Deficient circumferential growth is the primary determinant of aortic obstruction attributable to partial elastin deficiency. Arterioscler Thromb Vasc Biol 2017 May;37(5):930–41. https://doi.org/10.1161/ATVBAHA.117.309079. PMID: 28254817.

[8] Zhang Y, Lacolley P, Protogerou AD, Safar ME. Arterial stiffness in hypertension and function of large arteries. Am J Hypertens 2020 Apr1;33(4):291–6. https://doi.org/10.1093/ajh/hpz193. PMID 32060496.

[9] Morris CA, Braddock SR, Council on Genetics. Health care supervision for children with Williams syndrome. Pediatrics 2020 Feb;145(2). https://doi.org/10.1542/peds.2019-3761. pii: e20193761. PMID:31964759.
[10] Madueme et al — Segmental Approach.
[11] Tsuda et al. "Functional assessment of the left ventricle".
[12] Cha SG, Song MK, Lee SY, et al. Long-term cardiovascular outcome of Williams syndrome. Congenit Heart Dis 2019 Sep;14(5):684–90. https://doi.org/10.1111/chd.1281831166070.
[13] Ergul Y, Nisli K, Kayserili H, et al. Cardiovascular abnormalities in Williams syndrome: 20 year' experience in Istanbul. Acta Cardiol 2012;67(6):649–55. https://doi.org/10.2143/AC.67.6.2184667.
[14] Matisoff AJ, Olivieri L, Schwartz JM, Deutsch N. Risk assessment and anesthetic management of patients with Williams syndrome: a comprehensive review. Pediatr Anesth 2015 Dec;25(12):1207–15. https://doi.org/10.1111/pan.1277526456018.
[15] Davis TS, Epelman MS, Madueme, Bender KS, Dadlani GH. MRI detection of occult venous anomalies in a patient with Williams syndrome: a case report. Cardiol Young 2020 Apr;30(4):568–70. https://doi.org/10.1017/S104795112000030X. PMID: 32102714.
[16] Latham GJ, Ross FJ, Eisses MJ, et al. Perioperative morbidity in children with elastin arteriopathy. Paediatr Anaesth 2016 Sep;26(9):926–35. https://doi.org/10.1111/pan.1296727397140.
[17] Van Pelt NC, Wilson NJ, Lear G. Severe coronary artery disease in the absence of supravalvar stenosis in a patient with Williams syndrome. Pediatr Cardiol 2005 Sep-Oct;26(5):665–7. https://doi.org/10.1007/s00246-004-0845-815549615.
[18] Olsen M, Fahy CJ, Costi A, Kelly AJ, Burgoyne LL. Anasesthesia-related haemodynamic complications in Williams syndrome patients: A review of one institution's experience. Anaesth Intensive Care 2014 Sept;42(5):619–24. https://doi.org/10.1177/0310057X1404200512.
[19] Federici D, Ranghetti A, Merlo M, et al. Coronary artery involvement of Williams syndrome in infants and surgical revascularization strategy. Ann Thorac Surg 2016 Jan;101(1):359–61. https://doi.org/10.1016/j.athoracsur.2015.03.06426694280.
[20] Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics-2020 update: A report from the American Heart Association. Circulation 2020 Mar 3;141(9):e139–596. https://doi.org/10.1161/CIR0000000000000075731992061.
[21] Wahart A, Hocine T, Albrecht C, et al. Role of elastin peptides and elastin receptor complex in metabolic and cardiovascular diseases. FEBS J 2019 Aug;286(15):2980–93. Doi:10.111/febs.14836. 30946528.
[22] Flynn JT, Kaebler DC, Baker-Smith, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics 2017 Sep;14093. https://doi.org/10.1542/peds.2017-1904. Piie20171904. PMID: 28827377.
[23] Collins RT, Aziz PF, Swearingen CJ, Kaplan PB. Relation of ventricular ectopic complexes to QTc interval on ambulatory electrocardiograms in Williams syndrome. Am J Cardiol 2012 Jun 1;109(11):1671–6. https://doi.org/10.1016/j.amjcard.2012.01.395. PMID 22459308.
[24] Collins RT, Aziz PF, Gleason MM, Kaplan PB, Shah MJ. Abnormalities of cardiac repolarization in Williams syndrome. Am J Cardiol 2010 Oct 1;106(7):1029–33. https://doi.org/10.1016/j.amjcard.2010.05.04120854969.
[25] McCarty HM, Tang X, Swearingen CJ, Collins RT. Comparison of electrocardiographic QTc duration in patients with supravalvar aortic stenosis with versus without Williams syndrome. Am J Cardiol 2013 May 15;111(10):1501–4. https://doi.org/10.1016/j.amjcard.2013.01.308. PMID; 23433766.